REMARKS

Claims 1-65 are pending. Claims 9-49, 58-65 have been withdrawn from further consideration as being drawn to non-elected inventions. Claims 1-8, 50-57 are under examination. Claims 1 and 50 have been amended.

Applicants respectfully assert that all amendments are supported by the original disclosure and do not introduce new matter. Moreover, Applicants further respectfully assert that the amendments merely clarify the scope of the claims.

Objections withdrawn

Applicants appreciate Examiner's withdrawal of the previous objection to claims 44-49, 59-63, and 65 because the claims depend from a non-elected invention is withdrawn in view of applicant's withdrawn of the claims from further consideration.

Rejections Withdrawn

Applicants appreciate Examiner's withdrawal of the previous rejection of claim 7 under 35 U.S.C. 112, second paragraph for lacking antecedent basis in view of applicant's amendment to the claim.

Applicants appreciate Examiner's withdrawal of the previous rejection of claims 50-57 under 35 U.S.C. 112, first paragraph, because the phrase "are contacted with an acidic buffer" is considered new matter in view of applicant's amendment to the claims.

Applicants appreciate Examiner's withdrawal of the previous rejection of claims 1-8, 44-49,63, and 65 under 35 U.S.C. 112, first paragraph in view of applicant's amendment to the claims.

Applicants appreciate Examiner's withdrawal of the previous rejection of claims 1-8, 44-57, and new claims 59-63 and 65 under 35 U.S.C. 103(a) in view of the Declaration of Qi.

Applicants appreciate Examiner's withdrawal of the previous provisional rejection of claims 1-3, 44-47, 50-52 and new claims 59-61 and 65 in view of applicant's abandonment of the copending Application No. 10/967,921.

Claim Rejections - 35 USC § 112, 1st paragraph (Written Description)

The Examiner has maintained the rejection of claims 1-8 and 50-57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner contends that the amendment to the claims does not overcome the rejection for the following reasons:

The Examiner contends that the prior art and the Declaration of Qi show that the H1 and H5 helix regions are required for the function of retaining plasma membrane affinity, the claimed function is not retaining plasma membrane affinity, but an anti-tumor activity. The specification does not establish a correlation between plasma membrane affinity and anti-tumor activity.

Applicants have now amended the claims to provide for "wherein the polypeptide comprises a saposin fold and retains plasma membrane affinity." The saposin fold structure is described in paragraphs [0006] and [0007] of the original specification. As described in the specification, along with knowledge in the art, it would have been understood that the saposin fold was necessary structure for the activity of the present invention. The saposin fold comprises five alpha-helices (H1 through H5), which are responsible for proper orientation within the phopholipid bilayer of the nanovesicles and further comprise the enzyme activation domain of amino acids 48-62, which span helices H3 and H4.

While the Examiner points out that the specification has not shown that the plasma membrane affinity is the sole factor for the anti-tumor activity, the plasma membrane affinity is a necessity. Furthermore, the Examiner contends that while one of skill in the art could identify all of the nucleic acid sequences that encode a polypeptide with at least 95% sequence identity with SEQ ID NO: 2, the level of skill and knowledge in the art is such that one of ordinary skill in the art would not be able to identify without further testing which of those proteins having at least 95% identity to SEQ ID NO: 2 (if any) have the anti-tumor activity.

Applicants are confused by this rejection. Among the patent rules, there is no outright prohibition against experimentation. With respect to the Office's rejections under 35

USC § 112, First Paragraph, the applicants respectfully point out the goals of the written description requirement. These are 1) to clearly convey the information that an applicant has invented and the subject matter which is claimed and 2) to put the public in possession of what the applicant claims as the invention. *MPEP* §2163. There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim,* 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976).

As noted by the Office, satisfactory disclosure "depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." *Office Action, p.5, citing Revised Guidelines for the Written Description Requirement.* The Office is reminded that "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." *MPEP* § 2163.

Applicants respectfully assert that these requirements have been met, and that the disclosure adequately provides a written description such that one of ordinary skill in the art (which is deemed to be quite high) would be reasonably led to a particular species suitable for carrying out the claimed invention.

In fact, while the specification of the present application does not contain sequence listings for saposin C variants that have the ability to enact fusion of the nanovesicles with tumor cells and to activate apoptosis, the specification does provide for examples describing the use of the necessary domains and the changes that may be incurred. The changes to sequences of such specific examples using conservative substitutions are very well-known in the art. Further, the disclosure of sequences and domain sites further provides meaningful, specific guidance that would allow one of ordinary skill in the art to "immediately envisage" the claimed invention.

In *Fiers* v. *Sugano,* relating to an interference proceeding in which the court found that the *Fiers* application did not meet the written description requirement with regard to the following count: "a DNA which consists essentially of a DNA which codes for a human

fibroblast interferon-beta polypeptide," no such DNA sequence was disclosed in the *Fiers* application. The court held that the specification did not meet the written description requirement as conception of the claimed DNA did not occur upon conception of a method for obtaining it, but rather upon the inventor envisioning the detailed chemical structure of a gene so as to distinguish it from other materials and a method for obtaining the gene.

In contrast to the count at issue in *Fiers,* the present application discloses and relies upon sequences fully known in the art that are useful in the practice of the claimed invention, *i.e.,* the Saposin C sequences. Thus, Applicants respectfully submit that the present specification provides adequate written description of the present invention. Given the concededly high level of skill in the art, it would be a routine matter to one skilled in the art to isolate Saposin C variant sequences which incorporates the saposin fold and provides for both plasma membrane affinity and tumor killing activity.

Claim Rejections - 35 USC § 112, 1st paragraph (Enablement)

The Examiner has maintained the rejection of claims 1 -8, and 50-57 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a nanovesicle comprising a phospholipid selected from the group consisting of phosphatidylserine, phosphatidylethanolamine and structural analog thereof, and a polypeptide having an amino acid sequence at least 95% identical to SEQ ID NO:2, or a polypeptide of SEQ ID NO:2 having one or more conservative substitutions is maintained.

The Examiner contends that while the prior art and the Declaration of Qi show that the H1 and H5 helix regions are required for the function of retaining plasma membrane affinity, the specification does not establish a correlation between plasma membrane affinity and anti-tumor activity. The Examiner then contends that it would require undue experimentation to perform the invention as claimed.

Applicants respectfully disagree.

First, the Applicants have now amended the claims to provide for "wherein the polypeptide comprises a saposin fold and retains plasma membrane affinity." The saposin fold structure is described in paragraphs [0006] and [0007] of the original specification. As described in the specification, along with knowledge in the art, it would have been understood that the saposin fold was necessary structure for the activity of the present invention. The saposin fold comprises the H1 through H5 helices that are responsible for proper orientation within the phopholipid bilayer of the nanovesicles and further comprise the enzyme activation domain of amino acids 48-62, which span helices H3 and H4.

The activation region is discussed in the JBC paper from 2001 (276 (29), 27010-17) with Figure 1 having it underlined. This figure also shows that this region spans from Helix 3 to Helix 4.

Second, the determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. As set forth above, applicants have provided working examples that show the use of different Saposin C sequences to enact tumor cell killing. The determination of the appropriate protein sequence of possible variants would necessarily be determined empirically and would be considered merely routine in the relevant art.

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Here, any experimentation, if it in fact is deemed necessary, would be considered well within the ordinary course of the art and would not be considered undue.

An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. "The test is not merely quantitative since a considerable amount

of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands,* 8 USPQ2d at 1404 (CCPA 1076). The quantity of experimentation can be "considerable," "tedious," "laborious," and "time-consuming," as long as the experiments are merely "routine." Here, the specification clearly shows how to determine if a sequence is appropriate using only routine laboratory methods.

In fact, the specification meets the enablement requirements of § 112 for the full scope of the claims in that the application discloses the intended patients, therapeutically effective amounts of the composition to be administered, exemplary routes of administration, the intended therapeutic product, and the intended disease. The current application does not broadly claim all protein sequences without demonstrated, working examples. In fact, the specification provides multiple working examples showing striking results. These examples show that the claimed sequence was successfully delivered and resulted in a dramatic tumor killing activity.

At the time of filing the present application, protein sequencing techniques, particularly those using the Saposin C sequence, were known and practiced in the art. In fact, an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. "The test is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands,* 8 USPQ2d at 1404 (CCPA 1076). The time and expense are merely factors in this consideration and are not the controlling factors. The sequences that fall within the scope of the present claims are easily ascertained by any person skilled in the present art.

The scope of the claims requires that the Saposin C variant sequence is capable of activity of in cancer cell targeting and killing. For activity, the fusion of the SapC/DOPS nanovesicle is required to deliver SapC to the cell interior and the SapC must activate apoptosis. For the fusion process to occur it is known from the art (Qi and Grabowski, 2001) that SapC inserts into lipid bilayers due mostly to its amphipathic character. It is also know from the art that

the enzyme activation domain of SapC resides in residues 48-62 (Qi and Grabowski, 2001). Mutations that do not alter these functions within these regions would be potential candidates for molecules with similar activity.

The amphipathic character of the helices is dominated by the regularly spaced hydrophobic residues (Jones et al 1992, Epand, 1993). In the case of SapC these hydrophobic residues are dominated by the group Isoleucine, Leucine, Methionine and Valine. Since the hydrophobicity of these residues is similar (Jones et al 1992) it would be obvious to try permutations of these residues with the expectation of largely maintaining activity. The typical approach would be to make substitutions individually at each of these positions to see which are tolerated and test in a cell targeting assay. It would be preferred to substitute within the Ile, Leu, Met, Val groups and less preferred to try Phe as well.

The activation region for the enzyme is within residues 48-62 of Saposin C. The consensus sequence is described (Qi et al 1996) and the level of conservation here is pretty high, with 6 conserved, but 7 fairly conserved. Amino acid variations found within this region are claimed. These include V51L, D52G, D52V, Y54F, S56P, S56D, S56R, I58L, I58T, L59V, S60D, S60A, I61V, I61L and L62F.

Therefore, it is well within the scope of ability of one skilled in the art to test sequences of the present invention for the following reasons: (1) the amount of testing required is relatively small especially since most of the work can be done with tissue culture experiments as the proof of principle with the animal studies was already provided; (2) testing of any particular sequence in question would not require direction or guidance beyond that known in the art; (3) the current state of knowledge in the art and relative skill of those in the art is quite high; (4) well-known procedures exist for sequencing various protein sequences capable of producing the desired therapeutic effect; and (5) determining whether or not a sequence falls within the scope of the claims is quite straightforward since all of the materials and methods that would be required to determine if a particular sequence capable of producing the desired therapeutic effect are well known and practiced in the art.

In view of the amendments to the claims and Applicant's arguments set forth above,

applicants respectfully submit that the claims as pending do not require undue experimentation, and sufficiently meet the standard for enablement. As such, applicants respectfully request reconsideration and allowance of the claims.

Double Patenting

The rejection of claims 1-3, and 50-52 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 16, 17, 21 and 22 of U.S. Patent No. 6,872,406 in view of Vaccaro et al. (FEBS Lett. 1994, 349: 181-186, IDS) is maintained.

Applicants assert that a Terminal Disclaimer will be filed if conflicting claims are issued.

New Grounds of Objections and Rejections

Claim Objections

The Examiner has objected to claims 1-8 because of the following informalities: claim 1 recites "wherein the phospholipid forms a nanovesicle having the polypeptide embedded within its polypeptide embedded nanovesicle".

Applicants apologize for any lack of clarity. The claims have now been amended to read "wherein the phospholipid forms a nanovesicle having the polypeptide embedded within the phospholipids of the ~~its polypeptide embedded~~ nanovesicle."

Claim Rejections - 35 USC § 112, 1st paragraph

The Examiner has rejected claims 1-8 and 50-57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as a new matter rejection.

The Examiner contends that the phrases "wherein the polypeptide comprises H1 through H5 helix regions of saposin C and retains plasma membrane affinity" recited in claim 1, and "wherein the polypeptide includes sequences which form helix regions H1 and H5 of saposin C, which embed within the lipid bilayer of the nanovesicle" recited in claim 50 are considered new matter since the specification, drawings and claims as filed do not provide clear support for such limitations.

Applicants have now amended the claims to provide for "wherein the polypeptide comprises a saposin fold and retains plasma membrane affinity" .

Claim Rejections - 35 USC §103

The Examiner has rejected claims 1-8 and 50-57 under 35 U.S.C. 103(a) as being unpatentable over O'Brien (US 5,700,909, Date of Patent: 12/23/1997), in view of Liu et al. (WO 98/33482, Pub. date: 8/6/1998), and Habberfield (US 2002/0099001A1, Pub Date: 7/25/2002, earlier effective filing date 2/1/1995).

O'Brien teaches a method of treatment of demyelination disorders in mammal comprising administering to the mammal a pharmaceutically effective amount of saposin C, wherein the saposin C may be advantageously enclosed in a liposome-like (lamellar) structure (see column 4, lines 48-63, and column 9, lines 52-59). O'Brien discloses that the liposome encapsulation technology is well known (see column 9, lines 52-59). O'Brien discloses the amino acid sequence of Saposin C (SEQ ID NO:4) (see column 7, lines 4-5), which is 100% identical to the instant SEQ ID NO:2 (see sequence alignment, Exhibit A).

O'Brien does not teach that the liposome is made of phosphatidylserine, dioleoylphosphatidylserine (DOPS), or phosphatidylethanolamine. O'Brien does not disclose the recited molar ratio and mass ratio of saposin C to phospholipid. However, these deficiencies are made up for in the teachings of Liu and Habberfield.

Liu et al. teach encapsulation of a drug in liposome vesicle for in vivo drug delivery, wherein the liposome vesicle is a single bilayer or multiple bilayers vesicles consisting of phospholipids in which an aqueous volume is entirely enclosed by a membrane composed of lipid molecules, wherein the lipid is preferably phosphatidylcholine (PC), phosphatidylethanolamine (PE), or phosphatidylserine (PS) (see page 2, lines 28-30, page 3, lines 10-11), and the molar ratio of the drug molecules to the lipid is 1:2 to 1:20 or 1:2 to 1:100 (see page 3, lines 14-22). It is noted that according to the drug/lipid ratio of 1:2 to 1:100, the calculated mass ratio of the saposin C to the phosphatidylserine is 5:1-1:9. Liu et al. teach that the size of the liposome can vary from about 10nm to about 25 nm, (see page 6, lines 1-6, and claims).

Habberfield teaches liposomes composed of DOPS for drug delivery (see paragraph 0027).

The Examiner contends that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the liposome composed of phosphatidylserine such as DOPS or phosphatidylethanolamine to encapsulate saposin C with the molar ratio taught by Liu for the treatment of demyelination disorders in view of the teachings of Liu and Habberfield.

Although the cited references do not teach that the saposin/liposome nanovesicles comprising saposin C, and phosphatidylserine such as dioleoylphosphatidylserine or phosphatidylethanolamine have anti-tumor activity or promote death in cancer cells, the claims are drawn to a product per se and inherently, such nanovesicles would have anti-tumor activity. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252,195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Applicants respectfully disagree with the Examiner. The O'Brien reference teaches that peptides derived from Saposin C can be used to treated demyelination disorders. Although O'Brien discloses that the liposome encapsulation technology is well known, it is clear the treatment does not require the liposomes. Partial Saposin C sequence claimed by O'Brien is sufficient for the potential treatment. The invention of the present patent describes that the combination of Saposin C and DOPS is necessary for the anti-cancer activity. Saposin C or its peptides alone have no killing effect on cancer cells (see Table 1). Therefore, the present disclosure is not obvious by learning from O'Brien's patent.

The O'Brien patent cited claims for peptides from the first part of the peptide, not the full saposin C or the prosaposin. They specified for the peptides for nerve cell proliferation to

counteract degeneration. Our invention is the combination of Saposin C and DOPS for killing of cancer cells.

The examiner also listed two patents by Habberfield and Liu et al. for teaching liposomes composed of PS for drug delivery. Again, Saposin C is not an anti-cancer drug. We did not disclose a DOPS liposome delivery system for Saposin C. The anti-cancer effect, indeed, requires both composition of DOPS and Saposin C (see Table 1). For example, replacement of DOPS with DOPC does not kill cancer cells. Also, encapsulation of Saposin C in DOPS vesicle does not kill cancer cells either (Table 1).

In addition, Habberfield and Liu claimed that the encapsulation step is required for the drug delivery by the liposomes containing DOPS. In our patent application, Saposin C couples with the DOPS liposome by embedding its N- and C-terminal sequences into the lipid bilayer (see Figure 1 and References [1] X. Qi, and G.A. Grabowski, Differential membrane interactions of saposins A and C: implication for the functional specificity. *J. Biol. Chem.* (2001) 276 27010-27017. [2] Y. Wang, G.A. Grabowski, and X. Qi, Phospholipid vesicle fusion induced by saposin C. *Arch. Biochem. Biophys.* (2003) 415, 43-53). Such Saposin C-DOPS coupled complexes showed the anti-cancer activity. Membrane surface exposed Saposin C plays a critical role to induce cancer cell death. In fact, encapsulation of Saposin C by either DOPS or DOPC liposomes had no significant killing effect on cancer cells (see Table 1 and Figure 2). It is clear that Saposin C-DOPS complex is not same as the liposomes for drug delivery claimed by Habberfield and Liu et al.

Conclusion

In light of the amendments and remarks made herein, it is respectfully submitted that the claims currently pending in the present application are in form for allowance. Accordingly, reconsideration of those claims, as amended herein, is earnestly solicited. Applicants encourage

the Examiner to contact their representative, Stephen R. Albainy-Jenei at (513) 651-6839 or salbainyjenei@fbtlaw.com.

The Commissioner for Patents is hereby authorized to charge any deficiency or credit any overpayment of fees to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,

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